

REVIEW ARTICLE

Neuroprotective and neuroregenerative effects of *Sambucus nigra*: Mechanisms and therapeutic potential

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Abstract

An essential indicator of neurodegenerative diseases is progressive neuronal degradation, often leading to cognitive and motor deficits. Recent studies have highlighted the *Sambucus* genus, particularly *Sambucus nigra* (elderberry [EB]), commonly known as a black elder, as a promising source of bioactive compounds with potential neuroregenerative effects. This review evaluates the potential of EB in mitigating inflammation, oxidative stress, and neurodegenerative processes. EB's rich polyphenolic profile – including terpenoids, flavanols, and anthocyanins – has been shown to enhance antioxidant defenses, protect neurons from oxidative damage, and stimulate neurogenesis. Furthermore, bioactive compounds in EB have been found to promote the release of neurotrophic factors, which play a crucial role in neuronal survival and repair. However, challenges such as low bioavailability, limited blood–brain barrier permeability, and the lack of standardized dosing guidelines for EB must be addressed in the future studies. In this review, relevant articles were identified through keyword searches in PubMed and Web of Science, supplemented with reference mining and citation tracking. As this is not a systematic review, only those citations pertinent to the specific requirements of the review were included. Particular attention is given to the mechanisms by which EB-derived compounds may support autophagy and modulate the mammalian target of rapamycin complex 1 signaling pathway, two critical defense strategies against neurodegeneration. These findings provide a foundation for future investigations into the therapeutic potential of EB in managing neurodegenerative disorders.

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1. Introduction

Nutrition is a fundamental strategy for maintaining health and preventing disease, and edible berries have long been recognized for their medicinal properties.¹ Recent studies have highlighted the *Sambucus* genus, particularly *Sambucus nigra* (elderberry [EB]), commonly known as a black elder for their medicinal properties. It has been suggested that these anthocyanin-rich berries may possess significant chemopreventive qualities.² Dietary intake of anthocyanins has been shown to enhance the overall antioxidant defense capacity of human plasma.³ In addition, researchers are focused on identifying specific drugs capable of effectively suppressing angiogenesis,⁴ while

substantial research has evaluated dietary approaches to inhibit angiogenesis.^{5,6}

While angiogenesis plays a crucial role in various physiological and pathological processes, the therapeutic potential of *S. nigra* extends well beyond its influence on vascular growth. It offers significant promise in addressing neurodegenerative diseases, where similar oxidative stress and inflammation mechanisms contribute to neuronal damage. Researchers have discovered that the *Sambucus* genus possesses significant pharmacological properties,⁷ which can be used to treat musculoskeletal problems, metabolic disorders, respiratory disorders, and skin conditions.⁸ Furthermore, these plants are rich in bioactive compounds, with 425 secondary metabolites identified to date, primarily consisting of terpenoids and phenolic compounds.⁹ These compounds are strongly associated with anti-inflammatory and antioxidant activities.¹⁰ *S. nigra* L., in particular, contains a diverse array of volatile compounds, predominantly terpenoids, including monoterpenes, terpenoid oxides and alcohols, and a sesquiterpene.¹¹

In elderflower *n*-hexane extracts, terpenoids account for 84.4% of the total volatile content, with essential oils comprising approximately 90.4%.¹² Flavonol glycosides dominate the flavonoid profile in most elderflower genotypes, making up more than 90% of the total flavonoid content. Elderflowers are also found to contain a significant quantity of phenolic compounds, with the two primary phenolic acids – 5-O-caffeoylquinic acid (chlorogenic acid) and 1,5-di-O-caffeoylquinic acid – constituting over 70% of the total phenolic acid content. In contrast, EBs are renowned for their high anthocyanin concentration.¹³

Various factors can damage neurons in the central nervous system (CNS). A degeneration of the CNS neurons causes neurodegenerative diseases, which commonly impair cognitive function.¹⁴ Aging is among the primary risk factors contributing to the development of neurodegenerative disorders. Individuals with these illnesses are more susceptible to oxidative stress, inflammation, and neurotransmitter depletion as they age.¹⁵ Extracts from the *Sambucus* genus are thought to possess significant neuroprotective potential due to their high concentrations of polyphenolic compounds. Furthermore, the multi-target actions of these compounds may play a role in their potent neuroprotective effects against the complex processes involved in neurodegenerative diseases.¹⁶ This review evaluates the mechanisms underlying *S. nigra*'s neuroprotective activity, specifically its influence on oxidative stress and neuroinflammation. The bioactive compounds within *S. nigra*, their pharmacological properties, and evidence supporting their therapeutic

potential in diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are also discussed. Finally, the review concludes with an evaluation of future research possibilities and clinical application of this plant to manage neurodegenerative diseases.

2. Search strategy

This review selectively identified relevant studies from Web of Science and PubMed based on their relevance to the neuroprotective and neuroregenerative effects of *S. nigra*, as well as its underlying mechanisms of action and therapeutic potential in neurodegenerative diseases. Articles were selected according to scientific merit and the significance of their findings on the application of *S. nigra* in alleviating oxidative stress and neuroinflammation.

Studies were included if they were published within the past 10 years, ensuring the review captures recent research on this topic. Studies falling outside the defined time frame or not directly focusing on the neuroprotective effect of *S. nigra* were excluded. Although this narrative review does not use a systematic strategy, the literature selection was framed to provide a comprehensive overview of the field.

3. Neuroinflammation mechanisms affected by EB-derived compounds

An essential component of redox signaling is the controlled generation of reactive oxygen species (ROS) and nitric oxide (NO), which mediate physiological reactions. ROS and NO are generated in many cell compartments under typical physiological circumstances, contributing to signaling cascades and modulating essential cell functions. However, microglial cells produce considerable ROS and NO during inflammatory circumstances by inducing and activating nicotinamide adenine dinucleotide phosphate oxidase and inducible NO synthase. Microglial cells may produce ROS and NO independently when lipopolysaccharides (LPS) or interferon-gamma (IFN- γ) are present.¹⁷ In addition, the extracellular signal-regulated kinase 1/2 (ERK1/2) activation results in a cross-talk between the nuclear factor-kappa B (NF- κ B) and IFN- γ -stimulated Janus kinases/signal transducers and activators of transcription pathways triggered by LPS.¹⁸ In these cells, IFN- γ -induced NO was rapidly prevented by U0126, a selective inhibitor of mitogen-activated protein kinase 1/2, the kinases that phosphorylate ERK1/2. Microglia activation is triggered by the release of proinflammatory cytokines and chemokines, such as tumor necrosis factor-alpha (TNF- α), interleukin 1-beta (IL-1 β), and IL-6, along with the generation of ROS and NO.¹⁹

Botanical substances have shown neuroprotective benefits by inhibiting microglial activation. EB extracts

have been revealed to exhibit pro- and anti-inflammatory features²⁰ and a similar biphasic impact on cytokine production in dendritic cells.²¹ Inflammatory reactions and death of neuronal cells are also triggered by 3-Nitropropionic acid, which raises the striatal ROS content.²² Recent studies indicate that EB extracts reduce ROS levels in human skin keratinocytes²³ and colon cells.²⁴

The association between inflammation and neurodegenerative diseases is significantly influenced by inflammatory cytokines and mediators, such as ROS and TNF- α , which can be modulated by EB extracts.²⁵ EB is shown to reduce LPS or IFN- γ -induced ROS and NO production, with certain flavonoids and anthocyanins being particularly effective in modulating these pathways. Notably, anthocyanins, such as cyanidin-3-O-glucoside, significantly inhibited ROS production and oxidative stress in microglial cells, reducing the production of pro-inflammatory mediators, such as TNF- α and IL-6. These compounds exert their effects by downregulating the NF- κ B pathway, a critical regulator of inflammation. For example, quercetin, a flavonoid found in high amounts in EBs, has been shown to inhibit the activation of NF- κ B, thereby reducing the secretion of TNF- α , IL-6, and other pro-inflammatory cytokines. In one study conducted by Sul and Ra,²⁶ quercetin treatment resulted in a 30% reduction in the production of TNF- α in LPS-stimulated microglial cells. Similarly, cyanidin-3-O-glucoside has been found to inhibit the *in vitro* production of IL-6 by preventing the NF- κ B activation in endothelial cells exposed to inflammatory stimuli (Table 1).

In addition, these compounds regulate the anti-inflammatory and pro-inflammatory responses, exerting a biphasic effect on cytokine production. For example, EB extracts can induce anti-inflammatory cytokines,

such as IL-10, at low concentrations in dendritic cells. In contrast, they can downregulate the production of inflammatory cytokines at high concentrations, thus establishing a mechanism for regulating inflammation during neurodegenerative disease development.^{24,25}

EB is renowned for its high concentration of bioactive components, such as flavonoids and anthocyanins that exhibit potent anti-inflammatory and antioxidant properties. These bioactive substances are thought to modulate the pathophysiology of neurodegenerative diseases, including neuroinflammation and cell death. Flavonoids in EBs have been shown to directly suppress the production of pro-inflammatory cytokines, which are key contributors to chronic inflammation in the brain.

A prolonged activation of microglial cells indicates neuroinflammation, which produces excess amounts of pro-inflammatory cytokines, causing oxidative stress, mitochondrial malfunction, and the initiation of cell death pathways. In particular, the constant release of TNF- α can cause neurons to undergo both necroptosis and apoptosis. The bioactive components of EBs may lessen the activation of death receptors on neurons, which are responsible for initiating caspase-dependent apoptosis, by downregulating TNF- α and IL-1 β levels. This decrease in cytokine signaling may shield neurons from going through apoptosis by preserving mitochondrial integrity and inhibiting the production of pro-apoptotic proteins, such as cytochrome c.²⁷

The antioxidant properties of EBs play a crucial role in modulating oxidative stress, a key contributor to neuronal damage. Chronic neuroinflammation leads to ROS and reactive nitrogen species overproduction, exacerbating apoptosis and ferroptosis – an iron-dependent cell death triggered by lipid peroxidation. Rich in anthocyanins,

Table 1. Key bioactive compounds in *Sambucus nigra* and their neuropharmacological effects

Compound	Class	Primary sources	Neuroprotective mechanism	Reported effects
Cyanidin-3-O-glucoside	Anthocyanin	Elderberry fruit	ROS scavenging, NF- κ B inhibition	Reduction in oxidative stress and inflammation in microglial cells
Quercetin	Flavonoid	Elderberries, elderflowers	NF- κ B inhibition, cytokine suppression	Reduction in TNF- α , IL-6, and IL-1 β production
Myricetin	Phenolic compound	Aqueous extract of elderberries	Inhibits α -synuclein oligomerization	Potential protection against PD-related protein aggregation
Sambucosides A – F	Iridoid glycosides	Twigs of <i>Sambucus williamsii</i>	NGF secretion enhancement	Elevation of NGF release in C6 glioma cells
Chlorogenic acid	Phenolic acid	Elderflowers	Antioxidant activity, metal ion chelation	Protection of neurons from oxidative damage
Kaempferol-3-O-rutinoside	Flavonol glycoside	Elderflowers	Anti-inflammatory, antioxidant	General neuroprotection

Abbreviations: IL-6: Interleukin 6; NF- κ B: Nuclear factor-kappa B; NGF: Nerve growth factor; PD: Parkinson's disease; ROS: Reactive oxygen species; TNF- α : Tumor necrosis factor-alpha.

EBs have been shown to scavenge ROS and inhibit lipid peroxidation, a critical step in the initiation of ferroptosis. By counteracting oxidative stress, EBs may reduce the likelihood of ferroptosis and necroptosis, which are increasingly recognized as significant contributors to neuronal death in neurodegenerative diseases, such as AD and PD.

Furthermore, it has been suggested that the flavonoids in EBs modulate the NF- κ B signaling pathway, a critical regulator of inflammation. Activation of NF- κ B is triggered by pro-inflammatory cytokines and ROS, leading to the transcription of additional inflammatory mediators. By inhibiting NF- κ B activation, EBs may help disrupt the positive feedback loop of neuroinflammation, thereby mitigating neuronal injury.²⁸

4. Antioxidant properties of *Sambucus*-derived compounds

The *Sambucus* genus, mostly EB, is an excellent source of antioxidants, such as polyphenols.²⁹ These compounds present strong antioxidant features by donating hydrogen atoms, chelating metal ions, and scavenging free radicals.³⁰ Several studies have shown the antioxidant potential of EB. For example, EB extracts have demonstrated significant antioxidant activity *in vitro*, assessed using methods such as the 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay and the oxygen radical absorbance capacity assay.³¹

Studies conducted on *in vitro* brain cell lines have shown that *S. nigra* extracts effectively shield neural cells against oxidative stress by decreasing ROS levels, averting glutathione depletion, and regulating antioxidant enzyme activity.³² Natural substances, such as EB extracts, which reduce oxidative stress in the brain and exhibit antioxidant properties, may offer neuroprotective benefits.³³

The brain is more susceptible to ROS than other organs due to its exceptionally high oxygen demand, high lipid content, weak antioxidant defenses, and limited regenerative ability.³⁴ Oxidative stress is known as a primary player in the development of neurodegenerative disorders, triggering molecular pathways that lead to the progressive loss of appropriate structures and functions in neurons.³⁵ In AD, several findings suggest that oxidative stress plays a significant role in its pathogenesis. Elevated levels of advanced glycation end products and metal ions, which accelerate free radical production, are commonly observed. In addition, oxidized proteins, lipids, and nucleic acids are prevalent in AD brains, often appearing earlier than other pathological manifestations.

Amyloid-beta (A β) peptides can also directly and indirectly contribute to oxidative stress. The aggregates of

A β counteract the functions of the cell membrane, leading to membrane disintegration, accumulation of ROS, and cell lysis. Moreover, A β can induce inflammation and local immune responses, creating an oxidative microenvironment.³⁶ Studies have evaluated the antioxidative effects of EB-derived bioactive components on murine microglial cell line murine microglial cell line (BV-2), which are essential for the CNS immunological response and are associated with many neurodegenerative diseases.^{22,25}

Ethanollic EB extracts significantly reduced the production of ROS induced by LPS or IFN- γ in a dose-dependent manner. Among the bioactive components, the anthocyanins – cyanidin 3-O-glucoside and cyanidin chloride – are particularly effective in reducing ROS production in microglial cells. Quercetin emerged as the most potent flavonoid in mitigating microglial cell oxidative stress. Chuang *et al.*²² examined the differences in oxidative responses among various EB genotypes following stimulation with LPS or IFN- γ , a crucial mediator of ROS generation in microglial cells. The “Wyldeewood” extract, a type of EB extract, demonstrated antioxidant qualities by preventing IFN- γ -induced ROS production and reducing the expression of phosphorylated-ERK1/2. The researchers highlighted the intricate and genotype-specific effects of EB extracts on the oxidative processes of microglial cells. Furthermore, De Rus Jacquet *et al.*³⁷ examined the antioxidant properties of the *Sambucus caerulea* flower extract on rat cortical astrocytes. In the study, elderflower extract markedly triggered the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element pathway, a pathway involved in antioxidative processes, in the cortical astrocytes. Astrocytes originating from human-induced pluripotent stem cells displayed a comparable impact. Furthermore, astrocytes in mixed neuron-glia cultures extracted from the midbrain of rats enhanced Nrf2-mediated transcription after being treated with elderflower extract. The findings suggest that EB extract can stimulate cortical astrocytes to activate antioxidant responses, which are crucial for maintaining and protecting neurons in the CNS.³⁸

While *S. nigra*'s antioxidant activity is well documented, it is useful to contextualize these effects by comparing them with other more extensively studied berries, such as blueberries and cranberries, whose antioxidant activities are of particular interest. Blueberries are rich in anthocyanins and flavonoids, which have been shown to significantly inhibit oxidative stress and improve cognitive function in various neurodegenerative disease models. Similarly, cranberries possess high levels of flavonoids and proanthocyanidins, which exhibit potent antioxidant and anti-inflammatory activity, particularly in cardiovascular health.

In contrast, *S. nigra* stands out for its extremely high content of anthocyanins, such as cyanidin-3-O-glucoside, which have been found to exhibit potent antioxidant activity through ROS scavenging and lipid peroxidation prevention. Studies have shown that while blueberries and cranberries offer widespread antioxidant protection, *S. nigra* has a more substantial effect in reversing neuroinflammation due to its unique composition of polyphenolic compounds, including flavonoids and phenolic acids.^{39,40}

5. Neuroregenerative properties of *Sambucus*-derived bioactive compounds

Neurogenesis involves a complex series of biological processes in the brain leading to the *de novo* generation of neurons. In adult mammals, neurogenesis predominantly occurs in two regions: the subgranular zone of the dentate gyrus in the hippocampus and the subventricular zone of the lateral ventricles. In the subventricular zone, newly formed neurons migrate along the rostral migratory stream to the olfactory bulb, where they integrate into the pre-existing neural network. In the subgranular zone, neural stem cells (NSCs) produce new granule cells in the dentate gyrus, which mature and eventually incorporate into the hippocampal network. Adult-born neurons undergo several maturation phases before fully integrating into pre-existing brain networks, displaying distinct protein markers. Various factors influence adult neurogenesis, including physical activity, stress, aging, and environmental enrichment. Although the precise functional roles of neurogenesis in adult brains are still under investigation, it is believed to play a key role in multiple cognitive functions, such as learning, memory, and mood regulation.⁴¹

The ability of specific drugs, treatments, or interventions to promote neural regeneration, neural replacement, or repair of lost or damaged brain tissue is called neuroregenerative potential. Therefore, utilizing the neuroregenerative potential of both endogenous and exogenous factors may help with the development of novel therapeutic strategies to alleviate symptoms of neurodegenerative diseases, such as PD and AD. Plant-based bioactive compounds, particularly polyphenols, have shown significant promise in supporting neuroregeneration. Compounds extracted from the *Sambucus* genus have demonstrated the potential to boost neuroregeneration by stimulating the release of neurotrophic factors and enhancing the proliferation and differentiation of NSCs.⁴²

It has been demonstrated that extracts derived from the *Sambucus* genus can stimulate NSC proliferation and differentiation. The effect of methanolic extract from the

fruit of *Sambucus ebulus* on the growth and development of NSCs obtained from the neonatal hippocampus of rats in the presence of an oxidative environment created by high hydrogen peroxide levels was examined. The results indicated that *S. ebulus* extract boosted NSCs' proliferation rate compared to the control group, with the maximum proliferation rate achieved at a concentration of 500 µg/mL. Bioactive compounds of *S. ebulus*, including polysaccharides, lectins, anthocyanins, and steroids, may explain the reported protective impact on NSCs. Furthermore, Liu *et al.*⁴³ found that pluripotent embryonic stem cells (ESCs) can develop into neurons upon exposure to an extract derived from *Sambucus williamsii*. According to the researchers' three-step differentiation technique, the upregulation of neuron-related genes, such as *Nestin* and *Tuj1*, in the extract-treated group indicates a stronger influence on neuronal differentiation than the control group. Furthermore, extract treatment resulted in a steady increase in the percentage of neurons from P1 to P3 generations, as evidenced by the expression levels of *Nestin* and *Tuj1*. On the other hand, *Oct4* and *Sox2* expression levels decreased, suggesting that the ESCs were gradually committing to the neuronal lineage.

Bioactive compounds derived from *Sambucus* plants promote both the proliferation and differentiation of NSCs and the secretion of neurotrophic factors necessary for preventing cell death and promoting the growth and differentiation of neurons in the CNS. For example, Suh *et al.*⁴⁴ examined the chemical composition of *S. williamsii* twig varieties, further elucidating their potential neuroprotective and neuroregenerative properties. In addition to two known derivatives, the authors extracted and characterized six novel iridoid glycosides, naming them sambucusides A – F, and evaluated their neuroprotective properties through the induction of nerve growth factor (NGF) secretion in the C6 glioma cell line. NGF is an essential neurotrophic factor for neuronal survival, upkeep, and regeneration in the CNS and peripheral nervous system. According to the study, several substances significantly increased NGF levels by 147.0% compared to the control, indicating a significant neuroprotective effect. In short, the study concluded that *Sambucus*-derived bioactive compounds have demonstrated promising neuroregenerative potential by stimulating the release of neurotrophic factors and promoting the proliferation and differentiation of NSCs. Subsequent studies further confirmed the promising neuroregenerative potential of these compounds, providing compelling evidence for future studies exploring their therapeutic implications in neurodegenerative diseases.⁴³⁻⁴⁵ In the future, more studies are required to elucidate the molecular pathways

underpinning the neuroregenerative potential of these compounds and further confirm their effectiveness. In addition, assessing the synergistic effects of multiple bioactive compounds found in *Sambucus* plants may result in more effective neuroregenerative techniques.

Notably, the current knowledge on the potential neuroregenerative effects of *Sambucus*-derived compounds primarily originates from *in vitro* studies. Despite promising results, the lack of comprehensive *in vivo* or clinical studies limits their translational value. Therefore, future investigations prioritizing animal models and clinical trials are critical to assess the efficacy, safety, and pharmacokinetic profiles of these compounds in more complex biological systems.

6. *Sambucus*-derived compounds and neurological diseases

The development of multifactorial AD progresses through multiple overlapping pathways. Excessive neuroinflammation is caused by ROS-induced oxidative stress and the aggregation and deposition of A β (1 – 42).⁴⁶ Research on AD should focus on finding treatments that prevent the tau protein produced by oxidative stress from forming filaments in the brain.⁴⁷

Treatment options for AD are diverse. To date, five drugs have been approved by the United States Food and Drug Administration for AD management. These include the cholinesterase inhibitors: donepezil, galantamine, and rivastigmine. In addition, memantine works through a different mechanism. A cocktail medication combines memantine with a cholinesterase inhibitor for enhanced efficacy.

Beyond conventional pharmacotherapy, numerous natural compounds, including phytoestrogens, antioxidants, and polyphenols such as curcumin, have been investigated for their potential to reverse AD pathology. Anthocyanidins (ANTs) are capable of crossing the blood–brain barrier and have been shown to protect brain tissue from oxidative stress-induced apoptosis, mitochondrial dysfunction, and A β toxicity.⁴⁸ For example, tau-phosphorylation caused by A β (1 – 42) was reduced by a formulation of ANTs.⁴⁹ According to Belkacemi and Ramassamy,⁴⁸ cyanidin-3-galactoside, cyanidin-3-glucoside, and cyanidin-3-arabinoside, three lingonberry ANTs, shield cells against apoptosis induced by oxidative stress. Badshah *et al.*⁵⁰ also demonstrated that potent antioxidants, such as black soybean ANTs, might prevent the neurotoxicity caused by A β (1 – 42) in AD. Through the mitochondrial apoptotic pathway, ANTs may reverse AD pathology by modulating Bcl-2-like protein 4 (Bax), cytochrome c, caspase-9, tau-

proteins, and beta-site amyloid precursor protein cleaving enzyme 1.⁵¹

Further studies by Gutierrez *et al.*⁵² and Pacheco *et al.*⁵³ assessed the levels of nitrite/nitrate (NO_x), Na⁺, K⁺-adenosine triphosphatase, Ca²⁺-adenosine triphosphatase, and acetylcholinesterase activities in the cerebral cortex and hippocampus of AD mouse models. Their findings suggest that ANTs can delay the onset of dementia by regulating cholinergic neurotransmission and ion pump activity. The inhibition of Ca²⁺ homeostasis by the ANTs from *Aronia melanocarpa* resulted in the death of SH-SY5Y cells, especially when the cells are protected against A β (1 – 42).⁵⁴ These ANTs increased adenosine triphosphate levels and mitochondrial membrane potential while lowering the concentrations of intracellular calcium ions and ROS. They also downregulated cleaved *casp3*, *Bax*, *Cycs*, and *casp9* gene expressions, while upregulating calmodulin and Bcl-2 protein expression. In addition, the ANT malvidin and its 3-glucoside (opening) exhibited comparable protective effects against A β (1 – 40)- and A β (25 – 35)-induced neurotoxicity by maintaining Ca²⁺ homeostasis.⁵⁵

The impact of distinct *Sambucus* extracts on the modulation of mammalian target of rapamycin complex 1 (mTORC1) signaling and subsequent autophagy activity has been investigated, particularly under conditions of oxidative stress induced by tert-butyl hydroperoxide. As anticipated, increased ROS levels in the presence of tert-butyl hydroperoxide led to oxidative stress and a decrease in mTORC1 signaling activity. However, ethanolic and aqueous extracts from *S. nigra* did not alter mTORC1 activity, as indicated by the unc-51-like kinase 1 phosphorylation at S757, a critical marker for managing oxidative stress. In contrast, these extracts modulated the antioxidant defense system. According to this study, high levels of ROS inhibited mTORC1 activity *in vitro* and *in vivo*, while low levels increased mTORC1 signaling activity.⁵⁶ Modest mTORC1 activation may support neuronal function and cellular survival in this context. Since mTOR hyperactivation is associated with an increase in tau protein phosphorylation and contributes to the production of neurofibrillary tangles in AD, maintaining a delicate balance of mTOR activity is necessary to prevent neurodegeneration.⁵⁷

Furthermore, in contrast to the ethanolic extract, the aqueous extract of EBs slightly enhanced autophagy in response to oxidative stress, indicating that this process is only marginally activated in SH-SY5Y cells. This may be attributed to the potent antioxidant properties of both extracts. These findings partially support a recent study that demonstrated *S. nigra* fruit extract-induced autophagy in dysplastic oral keratinocytes.⁵⁸

Table 2. Role of *Sambucus nigra*-derived bioactive compounds in neurodegenerative diseases

Disease	Pathogenic mechanisms	Bioactive compounds involved	Mechanisms of action	Potential outcome
Alzheimer's disease	A β aggregation, tau hyperphosphorylation, oxidative stress, neuroinflammation	Anthocyanins (e.g., cyanidin-3-O-glucoside), quercetin	Low A β toxicity, low ROS production, low tau phosphorylation, NF- κ B pathway inhibition	Protection against neuronal apoptosis, memory, and cognitive function improvement
Parkinson's disease	α -synuclein aggregation, mitochondrial dysfunction, oxidative stress	Myricetin, anthocyanins	Low α -synuclein oligomerization, antioxidant defense activation	Reduction in dopaminergic neuron loss, neuroprotection
Cerebellar ataxia	Ataxin-7 aggregation, oxidative stress, and immune-mediated neurodegeneration	Phenolics, anthocyanins	Low oxidative stress, potential inhibition of protein aggregation, and low microglial activation	Amelioration of motor dysfunction, cerebellar protection

Abbreviations: A β : Amyloid-beta; NF- κ B: Nuclear factor-kappa B; ROS: Reactive oxygen species.

Further investigation in SH-SY5Y cells is needed to deepen our understanding of the specific mechanisms through which EB modulates the removal of abnormal protein aggregates, a crucial step in preventing neurodegeneration. In this context, myricetin, the primary phenolic compound in the aqueous extract of EB, has been shown to reduce the oligomerization of α -synuclein, thereby offering protective effects against PD.⁵⁹

Finally, it is worth noting that a wide range of neurological conditions involving cerebellar damage and ataxia as a primary clinical feature is collectively referred to as cerebellar ataxia (CA).⁶⁰ Similar to AD and PD, immune-mediated neuronal dysfunction, which can lead to significant cell death in the cerebellum, is one of the key pathophysiological mechanisms underlying the development of CA.⁶¹ Furthermore, oxidative stress, a well-established cause of immune dysregulation, has been shown to induce selective neuronal death in various neurodegenerative disorders, including spinocerebellar ataxia (SCA), such as SCA1, SCA2, and SCA3.⁶² Specifically, ataxin-7 aggregation in PC12 cells has been linked to a highly oxidative environment, increasing cell toxicity. This finding may help explain how oxidative stress contributes to the pathophysiology of SCA7.⁶³

Despite a lack of direct evidence regarding the effects of *S. nigra* on CA pathophysiology and specifically, ataxin-7 aggregation, it can be hypothesized that its bioactive compounds may offer therapeutic potential in this context. This hypothesis is primarily based on results from related neurodegenerative models. Given that protein aggregation and oxidative stress are common pathological features in all of these disorders, it is plausible that *Sambucus*-derived compounds' antioxidant and anti-inflammatory properties could exert similar protective effects by mitigating pathological features, such as microglial activation and ROS production. However, this remains speculative, and further *in vivo* studies specifically targeting ataxin-7

and SCA models are necessary to validate this proposed mechanism (Table 2).

7. Conclusion

Due to its remarkable concentration of antioxidative and anti-inflammatory compounds, such as anthocyanins, flavonols, and other polyphenolic substances, this study highlights the promising neuroprotective and neuroregenerative features of *S. nigra*. Similarly, it has been shown that modulating oxidative stress and neuroinflammation can prevent protein aggregation, demonstrating significant therapeutic implications in neurodegenerative disorders, such as AD and PD. Although *in vitro* studies suggest that *Sambucus* extracts have potential in this context, limited *in vivo* and clinical results present a major hurdle for clinical translation. Therefore, future studies should prioritize designing robust pre-clinical models – such as transgenic mouse models of AD (e.g., APP/PS1), PD (e.g., α -synuclein overexpression), SCA (e.g., SCA7 ataxin-7 aggregation models), and other less studied diseases including Huntington's disease – to validate the therapeutic potential of *Sambucus* extracts.

Furthermore, well-designed randomized, double-blind, placebo-controlled clinical trials are needed to assess the efficacy, optimal dosing, and safety profile of standardized EB preparations in human populations. However, several translational barriers must be acknowledged. These include the low bioavailability and poor blood–brain barrier penetration of phenolic compounds, variability in phytochemical composition across EB cultivars and preparation methods, and the lack of standardized dosing guidelines. To overcome these limitations, novel delivery systems (e.g., nanoemulsions or encapsulation techniques) and rigorous phytochemical standardization protocols may enhance reproducibility and clinical applicability. In conclusion, while *S. nigra* holds considerable promise as a neuroprotective agent, targeted pre-clinical and clinical

investigations, coupled with advances in formulation science, are essential to fully realize its therapeutic potential in the management of neurodegenerative diseases.

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Conflict of interest

The authors declare no conflict of interest.

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